NCS Hypothesis #8: Maternal Subclinical Hypothyroidism and Neurodevelopmental Disabilities/Adverse Pregnancy Outcomes

1. Maternal subclinical hypothyroidism during pregnancy results in changes in **neurodevelopmental trajectories** in the offspring.

1a. Interactions between maternal subclinical hypothyroidism and maternal/fetal environmental **exposures to endocrine disrupting/hormonally active chemicals** during pregnancy result in changes in neurodevelopmental trajectories in the offspring.

1b. Interactions between maternal subclinical hypothyroidism and maternal/fetal environmental **exposures to stress** during pregnancy result in changes in neurodevelopmental trajectories in the offspring.

2. Maternal/fetal environmental exposures during gestation result in changes in **neurodevelopmental trajectories** in children, at least in part, **via disruption of the maternal thyroid system**.

3. Maternal subclinical hypothyroidism during gestation results in **adverse pregnancy outcomes**, specifically **preterm birth** (delivery < 37 weeks) and **preeclampsia**.

General Information	
Broad Focus Area	Neurodevelopment and behavior; Undesirable outcomes of pregnancy: preeclampsia and preterm birth
Background and Justification	Convincing epidemiologic data show that suboptimal thyroid function in pregnancy is associated with impaired intellectual development. Two studies have shown an association between low thyroid hormone concentrations in early gestation and significant IQ decrements in children at 7 years and 10 months of age, respectively.[1,2] In 2004, the American Thyroid Association (ATA), along with the American Association of Clinical Endocrinologists, sponsored a workshop to address the "Impact of Maternal Thyroid Status on Pregnancy and Fetal and Childhood Development." A statement from this workshop published by the ATA concluded that, although the problem of hypothyroidism from iodine deficiency in the U.S. has largely been addressed, "there are still additional adverse outcomes for maternal health, maintenance of pregnancy, and child development that may occur as a result of overt maternal hypothyroidism, as well as subclinical hypothyroidism (normal serum thyroxine concentration and elevated serum TSH concentration), maternal hypothyroxinemia (depressed serum free thyroxine concentration), and the presence of thyroid autoantibodies."[3] The ATA highlighted several recent research findings, among which two are particularly relevant to this proposed hypothesis and need further data with regards to "magnitude," namely that: • "Pregnant mothers with overt or subclinical hypothyroidism are at an increased risk for premature delivery." • "The offspring of mothers with thyroid hormone deficiency or thyroid stimulating hormone elevation during pregnancy may be at risk of mild impairment in their intellectual function and motor skills."[3] Endocrine disruption, as a mode of action for the toxicity of chemicals, has been of

	increasing interest and concern over the past decade. Of particular interest are chemicals that have been demonstrated to alter thyroid hormone function in laboratory animals and in wildlife; there is much less information from studies that assess thyroid effects in humans.[4] A recent review listed 116 chemicals that have demonstrated some potential for interacting with thyroid hormone status.[5] While variations of endocrine parameters like thyroid dysfunction during the prenatal period and infancy appear to be associated with developmental disabilities in the literature, the threshold for manifestation of these effects is currently undefined. In addition, there are information gaps regarding the potential effects of hormonally active agents in the environment on the developing fetus via maternal endocrine disruption, as well as potential direct interactions with the fetus for agents that can cross the placental barrier. A recent conference that focused on evaluation of endocrine disruption within the National Children's Study investigated the issue of thyroid hormone function, as well as other endocrine effects. Scientists who participated in this workshop highlighted the potential for chemical exposures to cause subclinical hypothyroidism and/or subclinical hypothyroxinemia, and thus increase the risk for adverse health and developmental outcomes in children, as an important priority for the NCS.[6,7] Maternal depression is a disease that affects fetal health.[8,9] Although both psychological and biological explanations have been researched, the hormonal hypotheses have received more attention. Depression is known to be associated with hypothalamo–pituitary–adrenal (HPA) axis hyperactivity; and maternal stress, anxiety, or depression (factors regulated by peptides derived from the activated HPA axis) each affect birth outcomes.[10,11,12,13,14,15] Thus, increased HPA-axis activity may directly affect fetal growth. Clinical maternal hypothyroidism has also been linked to a number of adverse pregnancy outcomes including infertility, preeclampsia, placental abruption, postpartum hemorrhage, and associated perinatal morbidity and mortality with a high frequency of low birth weight and fetal death.[16,17] Subclinical hypothyroidism has been linked to eclampsia, preeclampsia, and gestational hypertension.[18] Thyroid hormone status (decreased free T4 and increased TSH) has also been found to be related to severity of preeclampsia and degree of low birth weight.[19] Moreover, preterm babies born to mothers with preeclampsia and hypothyroxinemia show evidence of lower thyroid hormone levels *in utero* and at the time of birth.[20,21] Therefore, there is evidence to support the premise that clinical hypothyroidism is involved with preeclampsia, preterm birth, and associated adverse outcomes in infants. Subclinical hypothyroidism and/or hypothyroxinemia may be implicated as well, but the situation is less clear.
Prevalence/ Incidence	Of approximately 4,000,000 children born in the U.S. each year, it is estimated that 44,190 of these children are affected by mental retardation.[22] Cerebral palsy affects approximately 0.2% of children,[23] and autism affects about 0.3%.[24] The prevalence of cerebral palsy in the United States is increasing, due to the increased survival of very low and low birth weight infants.[25] Autism spectrum disorder also appears to be increasing in prevalence (6.7-16.8 per 1000 births[26,27]), and some neuropsychologic conditions of childhood, such as ADHD, are diagnosed at an epidemic rate (100-150 per 1000 children[28,29]). Adverse birth outcomes are more prevalent than neurodevelopmental disabilities.

	Each year in the US, approximately 12% of all births are preterm (<37 weeks gestation).[30] Preeclampsia occurs in approximately 8% of all pregnancies.[31]
Economic Impact	While no studies have precisely calculated all of the costs associated with autism, a U.K. report estimates the lifetime custodial costs of autism spectrum disorders in the range of $3-$4 million per child, with societal costs likely to be triple the individual estimate.[32,33] The lifetime economic costs of cerebral palsy have been estimated at $11.5 billion per annual cohort.[34] An internal NICHD report determined that the costs of neurobehavioral disorders in the U.S. are considerable, with an estimated annual economic burden exceeding $141 billion (in 2003$): $0.8 billion for impaired cognitive development as a result of mercury exposure, $49.0 billion for impaired cognitive ability due to nonpersistent pesticide exposure, $51.2 billion for mental retardation, and $40.6 billion for autism spectrum disorders.[35] Sixty-nine percent of LBW children are born preterm.[36] A report based on 1988 data estimated an annual incremental increase of $6 billion in health care, education, and child care costs attributable to children <15 years born low birth weight (LBW), compared to if they had been normal-birthweight.[37] This underestimates current costs because of increasing preterm birth rates and improved survival of preterm infants. Due to large socioeconomic and racial or ethnic disparities, the US population does not evenly share the medical, educational, and economic costs of preterm births. An April 2004 internal NICHD report estimated the annual burden of LBW to be $13.1B in 2003 dollars and that a four to seven percent reduction would save from $0.5-0.9 billion annually.[35]

Exposure Measures	
Primary/ Maternal	Maternal thyroid status - L-thyroxine (T4) - Free thyroxine (free T4) - L-triiodothyronine (T3) - Thyroid stimulating hormone (TSH) - Thyroid gland enlargement Maternal exposures to endocrine disrupting chemicals - PCBs - Dioxins/Furans - Pentachlorophenol - EBDCs and ETU - PBDEs - PFCs - Perchlorate Maternal stress during pregnancy - Stress hormones (e.g., cortisol) - Report of stressful situations, anxiety, or depression
Methods	- Biological specimens: Blood, urine, saliva, breast milk

Outcome Measures	
Primary/ Child	Neurodevelopmental trajectories, via neurocognitive and developmental tests - IQ - Domain-specific - Attention/concentration - Executive function - Learning and memory - Motor skills Preterm birth: - Gestational age; birth weight
Methods	Neurological exam Clinical and observational tests:

	- Examination by a medical professional - Interview		- Bayley Scales of Infant Development - Wechsler Preschool and Primary Scale of Intelligence - Wechsler Abbreviated Scale of Intelligence - Conners Rating Scale - Trail Making Test - Bender-II Recall - Purdue Pegboard Revised Examination by a medical professional
Life Stage	Repeated measures: preconception, 1st through 3rd trimesters, birth, and during nursing period	Life Stage	Birth; 1, 6, 12, and 18 months; 3, 5, 7, 9, 12, 16, and 20 years
Primary/ Child	Fetal thyroid status - L-thyroxine (T4) - Free thyroxine (free T4) - L-triiodothyronine (T3) - Thyroid stimulating hormone (TSH) Fetal exposures to endocrine disrupting chemicals - PCBs - Dioxins/Furans - Pentachlorophenol - EBDCs and ETU - PBDEs - PFCs - Perchlorate	***Secondary/ Child***	School performance
Methods	- Umbilical cord blood culture/pathology - Blood samples	Methods	School record examination for grades/performance
Life Stage	Repeated measures: At birth, during infancy	Life Stage	Follow-up in year 7, 9, 12, 16, and 20
Secondary/ Maternal			
Methods			
Life Stage			

Important Confounders/Covariates	
Child's exposure to neurotoxicants during childhood (e.g., lead)	Increased exposure to other neurotoxins would increase adverse neurodevelopment behavior.[38,39]
Family history	Twin and family studies have suggested a genetic link, which may be shown through family histories, to neurodevelopmental disorders.[40]

Mother's medical and obstetrical histories	Particularly in cases without a family history, various obstetric complications are often cited as possible causes for fetal neurodevelopmental disruption and consequent disorders.[41]
Economic status	Increased risk of preterm birth is associated with low educational level; unmarried status.[42]
Race/ethnicity	As a percent of live births, 17.6% among Blacks are preterm, 11.4% among Hispanics, and 10.8% among Whites.[43]
Mother's medical history	Increased risk of preterm birth is associated with maternal smoking, alcohol consumption; older maternal age (indicated preterm births); younger maternal age (spontaneous preterm births); low or high parity; previous stillbirth.[44,45,46]
Others	Increased risk of preterm birth is associated with caffeine consumption; unwantedness of the pregnancy.[47,48]

Population of Interest	Estimated Effect that is Detectable
All children	Assuming 100,000 infants born into the study, with an exposure prevalence of 2%, the smallest detectable relative risk would be, for cerebral palsy, 2.8; and for autism, 2.4.

Other Design Issues	
Cost/Complexity of Data Collection	- Thyroid examinations are routinely conducted on nearly every birth in the U.S. as part of neonatal screening programs conducted by state health departments. - Endocrine disruptors can be measured in archived samples retrospectively to minimize costs.
Cost of Sample Analysis	Analyses to detect the presence of endocrine disruptors in collected samples will be costly.

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